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Cytotoxic Effects of Ficus Carica L. Fruit Extract on T98G Glioblastoma Cells: An MTT-based Cell Viability Assessment

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ABSTRACT: Glioblastoma multiforme (GBM) is the most aggressive primary malignant brain tumour in adults with a high rate of recurrence and poor response to standard therapy. Fig fruit (Ficus carica L.) has been reported to have anticancer potential, but little is known about its effects on glioblastoma cells. In this study, the cytotoxic effect of Ficus carica L. fruit extract on T98G glioblastoma cells was evaluated by MTT assay. T98G cells were treated with 0.25, 0.5 and 1% (v/v) of Ficus carica fruit extract for 24–144 h. Cell viability was determined by the MTT assay performed in triplicate. Differences between groups were analysed statistically (one-way ANOVA, followed by Tukey's post-hoc test). Ficus carica fruit extract at all concentrations tested significantly reduced the viability of T98G cells when compared to the untreated control group ($p = 0.000$). The 1% concentration was the most potent in terms of cytotoxic effect and significantly different from the 0.25% and 0.5% concentrations ($p = 0.008$). Ficus carica L. fruit extract exhibits a dose-dependent cytotoxic effect on T98G glioblastoma cells, with the most prominent activity at 1% concentration. These results suggest that Ficus carica could be a candidate anticancer agent against glioblastoma, but more mechanistic and in vivo studies are needed.

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1. INTRODUCTION

Glioblastoma multiforme (GBM) continues to be the most aggressive and devastating primary brain tumour in adults, characterised by rapid proliferation, diffuse infiltration, and marked resistance to conventional therapies. Despite multimodal treatment, including maximal safe surgical resection followed by radiotherapy and temozolomide (TMZ) chemotherapy, median overall survival is limited to 12–18 months, with a five-year survival rate of <10%. The T98G cell line, which is from a human glioblastoma multiforme and is relatively resistant to TMZ, serves as a common in vitro model for the evaluation of novel therapeutic agents against this malignancy. The ongoing therapeutic difficulties underscore the critical need for alternative or adjunctive agents that can achieve selective cytotoxicity in GBM cells [1].

Natural products, particularly those derived from plants that contain polyphenols, flavonoids, and other bioactive compounds, have garnered increasing interest as potential sources of anti-cancer agents. This is attributed to their multi-targeted mechanisms, relatively favourable safety profiles, and capacity to overcome chemoresistance. Among these, Ficus carica L. (commonly known as the fig), a member of the Moraceae family with a long-standing history of ethnomedicinal use, has demonstrated promising antineoplastic activities across various types of cancer. Recent systematic reviews indicate that extracts from different parts of F. carica influence critical oncogenic pathways associated with cell proliferation, cell-cycle regulation, apoptosis, autophagy, invasion, and angiogenesis [2, 3].

Specifically, the MTT test has shown that extracts from the fruit of F. carica consistently exhibit cytotoxic and antiproliferative actions on a variety of human cancer cell lines. Fruit extracts in methanol and other solvents decreased the viability of Huh7it hepatocellular carcinoma cells, caused necrosis and apoptosis, and showed dose-dependent action; in certain models, leaf extracts were more potent. Fruit extracts also showed antiproliferative activity against colorectal cancer lines (HCT-116 and HT-29), HepG2 liver cancer cells, and MCF-7 breast cancer cells. These effects were frequently linked to the induction of apoptosis, increased levels of reactive oxygen species (ROS), and mitochondrial dysfunction. With little harm to normal pancreatic epithelial cells, F. carica fruit extract decreased cell viability, migration, invasion, and colony formation in pancreatic cancer models in a dose- and time-dependent manner. It also induced autophagy and senescence [4, 5].Previous studies showed the anti-proliferative and anti-invasive effects of F. carica latex in GBM cell lines such as T98G, U-138 MG, and U-87 MG through mechanisms involving apoptosis and modulation of microRNAs such as let-7d; however, there are limited reports assessing the cytotoxic potential of the fruit extract on T98G glioblastoma cells. Moreover, recent studies have validated the broader anticancer effects of fruit-based preparations using MTT-based viability and related assays in different types of cancer, providing a rationale for further studies in GBM models [6].

The known cytotoxicity of Ficus carica fruit extracts against various solid tumours, combined with the clinical need for effective agents against TMZ-resistant glioblastoma (GBM), has prompted the present study. This research is designed to evaluate the cytotoxic effects of Ficus carica L. fruit extract on T98G glioblastoma cells through an MTT-based cell viability assay. The objective is to demonstrate dose- and time-dependent reductions in cell viability, thereby providing preliminary evidence for the potential use of fig fruit extract as a natural cytotoxic agent against glioblastoma.

2. MATERIALS AND METHODS

2.1 Study Design

The experimental strategy used in this study is typified by a randomised control trial methodology. It comprises a control group as well as treatment groups that will be examined for variations in the suppression of T98G glioma cell lines grown on different media. 24 cell culture mediums were used in this study's post-test-only control group design. Three treatment groups (FC Extract doses of 0.25%, 0.5%, and 1%) and a control group (no treatment) made up the experimental design [7, 8].

2.2 *Preparation and Standardisation of Ficus carica L. Fruit Extract*

The fresh fruits of Ficus carica L. were harvested when ripe, subsequently washed and dried. Approximately 1 kg of the dried fruit material was macerated with 96% ethanol at room temperature for three 24-hour periods, with occasional stirring. The resulting filtrate was obtained through filtration and concentrated under reduced pressure using a rotary evaporator, maintained at a temperature of 50°C, with a rotation speed of 70 rpm and a pressure of about 175 mbar, yielding a thick crude extract [9, 10]. This concentrated extract was then diluted in culture medium to create working solutions at final concentrations of 0.25%, 0.5%, and 1% (v/v). Phytochemical screening was conducted at the Phytopharmacy Laboratory, Universitas Muslim Indonesia,

employing standard colourimetric reagents to identify major secondary metabolites. Additionally, antioxidant activity was assessed using the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging method. The extract was stored in the dark at 4°C until required. Given that the composition of plant extracts can vary based on harvesting conditions, geographical origin, and extraction parameters, this preparation underwent phytochemical screening to provide a basic qualitative profile of the bioactive constituents [9,10].

2.3 Cell line and Culture Conditions

The human glioblastoma cell line T98G was purchased from the American Type Culture Collection (ATCC). T98G cells were isolated from a 61-year-old Caucasian male and are frequently utilised as an in vitro model for assessing drug effects on glioblastoma, including TMZ-resistant phenotypes [11, 12]. The cells were cultured in the appropriate culture medium in standard conditions (37°C, 5% CO_2, humidified atmosphere) and subcultured according to the supplier's instructions. Only cells in the logarithmic phase of growth were used for experiments.

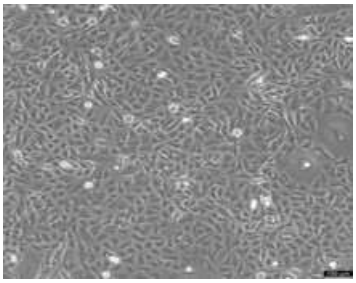


Figure 1. Cell line morphology T98G

2.4 Morphological Observation

The morphology of T98G cells was observed under an inverted phase contrast microscope (Optika, Italy). Representative fields from each treated group and untreated control were captured at 20× magnification with a digital camera (Optika, Italy) and stored using OptikaSview imaging software. Observations were concentrated on changes consistent with apoptosis or cytotoxicity, including cell shrinkage, rounding, membrane blebbing, cytoplasmic vacuolisation and loss of adherence [13,14].

2.5 MTT Assay Procedure

The MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay was used to determine the cell viability. T98G cells were plated into 96-well plates and allowed to attach. The culture medium was replaced after adherence with medium containing Ficus carica fruit extract at final concentrations of 0.25%, 0.5% or 1% (v/v) or fresh medium alone (untreated control). Treatments were administered for the specified periods (24, 48, 72, 96, 120 and 144 h). At each scheduled time point, the medium was carefully aspirated, and 100 L of MTT solution was added to each well under dim light conditions. Plates were incubated at 37 °C for 4 h to allow formazan crystal formation by metabolically active cells. Then, 200 μL dimethyl sulfoxide (DMSO) was added to each well, and the plates were gently shaken for 15 minutes at room temperature in the dark for dissolving the formazan crystals. Absorbance was determined at 620 nm using an ELISA microplate reader (Thermo Scientific Multiskan GO UV/VIS, USA). Assays were performed in triplicate. Results are expressed as mean absorbance ± SD. Lower absorbance values indicate lower metabolic activity and therefore lower cell viability [15-17].

2.6 Statistical analysis

Data Analysis: Effect of Fig Extract on Activity of Glioblastoma Cancer Cells by Using IBM SPSS This study will be done using a parametric test to examine the effect of fig extract on the apoptosis of glioblastoma cells in multiple groups of cell culture medium using inverted microscopy and MTT assay. The data obtained will be evaluated using normalcy and homogeneity. After checking for normal and homogeneous data distribution, a one-way ANOVA test will be used, followed by a post-hoc Tukey test, using SPSS version 16. The normality test is used to assess if the data is normally distributed or not. The normality test is based on the criteria of the significance level (sig) > 0.05. If data are not normally distributed, data will be transformed. If the data transformation results are normal. Then a one-way ANOVA test is performed to prove that there is a

significant difference between control and treatment ($P<0.05$), and a post-hoc Tukey test is performed to find out which variables have significant differences [18].

3. RESULTS AND DISCUSSION

This study is an in vitro investigation aimed at analysing the effect of fig extract on apoptosis in glioblastoma cells within T98G cell culture media. The research employs cell culture imaging using an inverted microscope and quantifies cell apoptosis through the MTT assay.

3.1 Results of *Ficus carica* L. Fruit extraction

The fig extract (*Ficus carica*) has undergone several stages of preparation, resulting in a thick liquid that has been tested for its chemical composition at the Universitas Muslim Indonesia Phytopharmacy laboratory. This extract was subsequently diluted to concentrations of 0.25%, 0.5%, and 1% for the evaluation of its effects on the T98G cell line culture, using inverted microscopy and the MTT assay.

Figure 2. Ficus carica L. Fruit extract and extract test concentration on T98G cells

The active substance content of fig extract was tested at the Phytopharmacy laboratory of Universitas Muslim Indonesia using phytochemical screening methods and antioxidant testing by DDPH. The DPPH (2,2-diphenyl-1-picrylhydrazyl) method for testing antioxidant activity is one of the most common and widely used methods for measuring antioxidant activity and the free radical capture activity of a sample. This method has some advantages, such as high accuracy, ease of obtaining and performance, speed, sensitivity and relative inexpensiveness. The results are shown in Table 1.

Table 1. Chemical Composition of *Ficus carica* L. Fruit Extract

No	Compound	**Reagents**	**Results**	**Literature**
1	**Alkaloid**	Dragendorff	(+)	Light Brown to Yellow
2	**Flavonoid**	$AlCl_3$	(+)	Yellow
3	Tanin	$FeCl_3$	(-)	Green-Blackish
4	Saponin	Hot Water + Concentrated HCL	(-)	Foam does not disappear after the addition of concentrated HCL

From the results of the examination of the content of active substances of fig extract, the content of Alkaloids and Flavonoids was determined.

3.2 Overview of Apoptosis through an Inverted Microscope

The fig fruit extract was categorised into four groups: extracts with concentrations of 0.25%, 0.5%, and 1%, along with a negative control group that received no treatment. The extract was administered simultaneously at each time point, spanning from day one (24 hours) to day six (144 hours). For each time point and concentration, the same MTT test was conducted with three replicates (triplicates). The results of cell apoptosis observed through an inverted microscope are presented in figures 2. The observations using the inverted microscope corroborate the MTT test results, revealing that the cells exhibited morphological changes such as rounding and shrinkage, alongside other forms including cell swelling, cytoplasmic vacuoles, and uneven structures and distribution of cells. This confirms apoptosis as a process that halts proliferation and activates cell death.

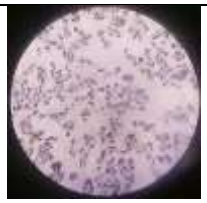
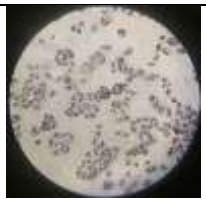
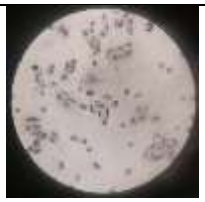
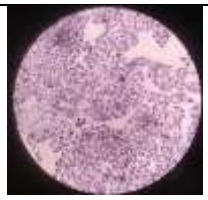
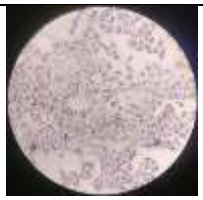
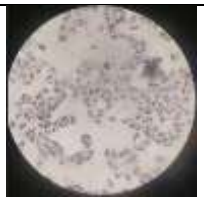
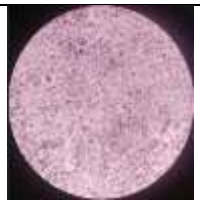
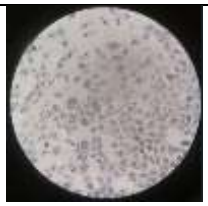
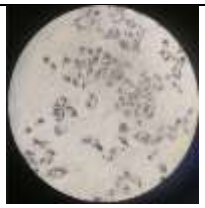
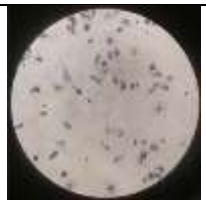
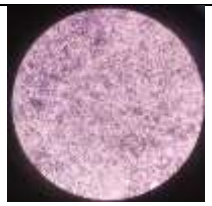
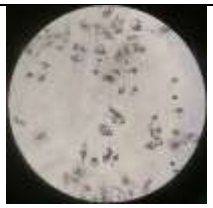
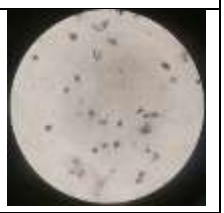
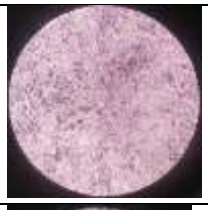
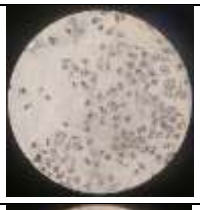
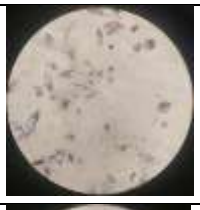
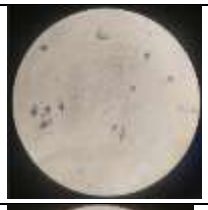
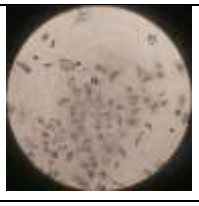
Time (Hours)	Control	0,25%	0,5%	1 %
24				
48				
72				
96				
120				
144				

Figure 2. Apoptosis *of T98G cell lines* through inverted microscope with formazan.

Figure 2 shows a significant decrease in the viability of the T98G cell line at 144 hours, especially in the 1% concentration group compared to the 0.25% and 0.5% concentration groups, characterised by an image of the apoptosis process. At early stages of apoptosis, T98G cells start to shrink and become rounded with some blebbing of their surface. The cell nucleus will become denser and may begin to fragment. Apoptosis continues with the breakdown of the cells into small apoptotic bodies. These bodies will look like small bubbles of solid cellular matter that are detached from the stem cells.

3.3 MTT Assay *Test Results* on Apoptosis *Cell Line* T98G

The MTT assay was utilised to evaluate apoptosis in the T98G glioblastoma cell line. Assessments were conducted at 24, 48, 72, 96, 120, and 144 hours following the administration of three different treatment groups of Ficus carica, alongside one negative control group that received no treatment. The results of the apoptosis test, as determined by the MTT assay, are presented in Table 2 and Figure 3 and 4.

Table 2. Comparison of MTT Assay Results for Apoptosis in T98G Cells among Treatment Groups

Time	Average Concentration (Mean)				
(Hours)	0,25%	0,5%	1%	Control	
24	0,1854	0,1608	0,1433	0,2730	
48	0,2787	0,2579	0,1468	0,5918	
72	0,1933	0,1604	0,0619	0,4487	
96	0,2011	0,1518	0,0393	0,4902	
120	0,2375	0,1193	0,0123	0,6071	
144	0,1873	0,1345	0,0077	0,6728	

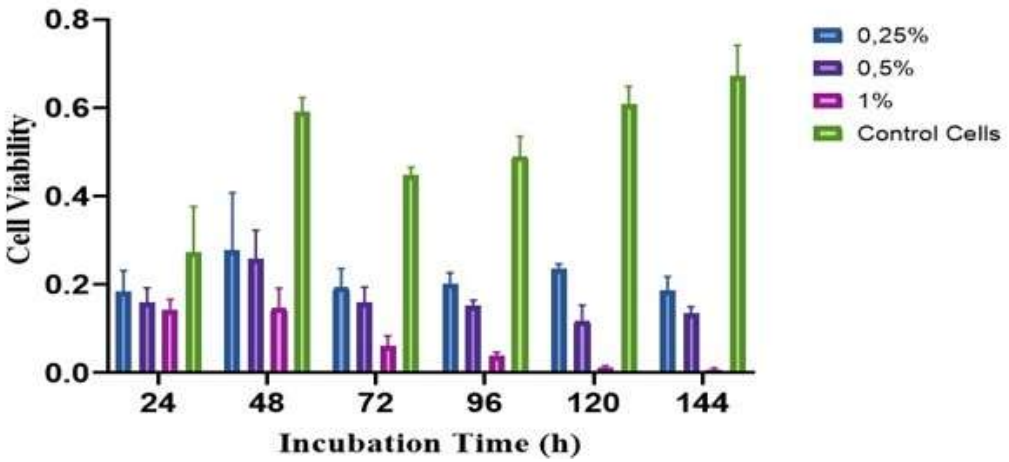


Figure 3. Comparison Diagram of MTT Assay Results on Apoptosis Cell Line T98G with Fig Extract Concentrations of 0.25%, 0.5%, and 1% and No Treatment.

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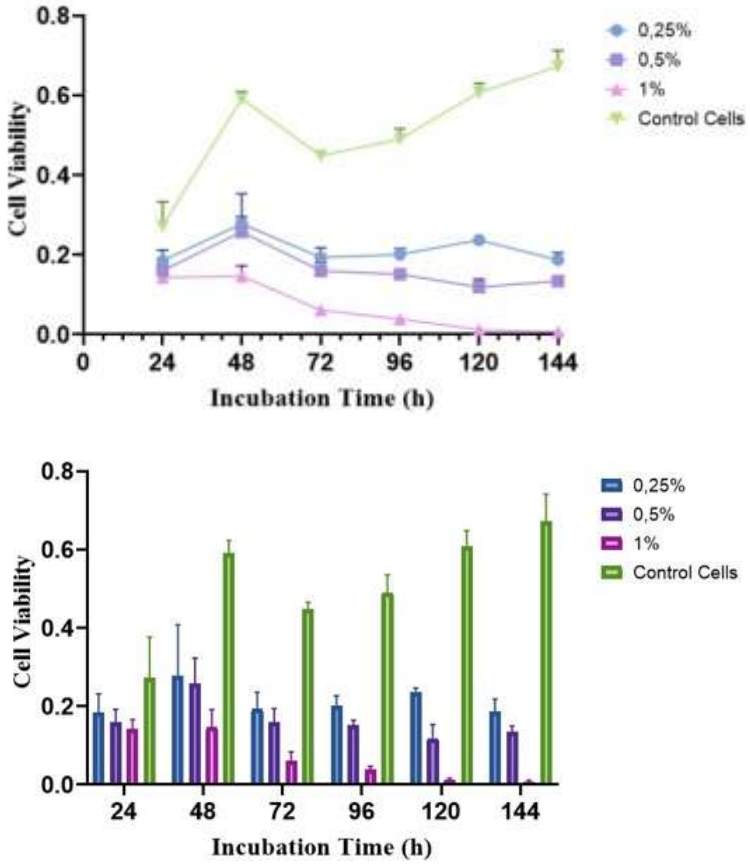

Figure 4. Graph of Cell *Line* Viability T98G in *MTT Assay* Test Against Fig Extract Test Group

The viability test (apoptosis) conducted on the T98G glioblastoma cell line using fig extract at various concentrations (0.25%, 0.5%, and 1%) demonstrated a reduction in cell proliferation following treatment at intervals of 24, 48, 72, 96, 120, and 144 hours. The overall viability of the T98G cell lines decreased across all groups treated with fig extract concentrations (0.25%, 0.5%, and 1%) when compared to the control group (which received no treatment). The most significant reduction was noted in the T98G cell line group treated with 1% fig extract, relative to the 0.25% and 0.5% groups.

3.4 Statistical Analysis

The Shapiro–Wilk normality test indicated that data in all groups were normally distributed ($p > 0.05$ for every group; Table 3). Consequently, parametric analysis was appropriate.

Table 3. Shapiro–Wilk normality test results

Groups	**Statistics**	**Value p**
Control negative	0.897	**0.315**
0,25 %	0.825	0.071
0.5%	0.878	0.216
1 %	0.877	0.212

Shapiro-wilk normality test, *$p > 0.05$: signifikan

One-way ANOVA revealed a highly significant overall difference in mean cell viability among the four groups (p = 0.000; Table 4). Mean absorbance (± SD) decreased with increasing extract concentration: control 0.529 ± 0.137, 0.25% 0.224 ± 0.043, 0.5% 0.173 ± 0.050, and 1% 0.068 ± 0.056.

Table 4. Mean viability (absorbance) of T98G cells and overall ANOVA result

Groups	**Mean±SD**	***p*- Value**
Control negative	0.529 ± 0.137	**0.000***
0,25 %	0.224 ± 0.043	
0.5%	0.173 ± 0.050	
1 %	0.068 ± 0.056	

One Way ANOVA, Mean, SD: Standard Deviation, *$p < 0.05$: signifikan

Tukey's post-hoc test showed that all three concentrations of extract resulted in a significantly lower viability than the untreated control (p=0.000). In comparison between the treatment groups, the 1% concentration was significantly different from both the 0.25% and 0.5% concentrations (p = 0.008), while the difference between 0.25% and 0.5% was not statistically significant (Table 5). These results support a concentration-dependent cytotoxic effect with the highest activity observed with the 1% extract under the test conditions.

Table 5. Tukey HSD post-hoc pairwise comparisons of cell viability

Comparison	**Mean difference**	**p-value**
Control vs all treatments	—	**0.000***
0.25% vs 0.5%	Not significant	0.649
0.25% / 0.5% vs 1%	Significant	**0.008***

$p < 0.05$ indicates statistical significance (Tukey HSD).

3.5 Discussion

MTT Assay Test of Fig Extract against Apoptosis Cell Line Glioblastoma T98G.

The results of the current study indicated that the ethanolic extract of Ficus carica L. fruit decreased the viability of T98G glioblastoma cells in a concentration-dependent manner, as assessed by the MTT assay. The 1% concentration exhibited the maximum toxicity, significantly surpassing the effects observed at the 0.25% and 0.5% concentrations. Morphological changes consistent with apoptotic or cytotoxic events were observed under inverted microscopy, supporting the quantitative findings of the MTT assay. These results align with previously reported cytotoxic activity of F. carica extracts on various cancer cell lines, including models of hepatocellular, colorectal, breast, and pancreatic carcinoma, as well as studies utilising F. carica latex on glioblastoma lines. Phytochemical screening revealed the presence of flavonoids and alkaloids, which may provide a plausible chemical basis for the observed activity, given that these classes of compounds are widely associated with the induction of apoptosis, generation of reactive oxygen species, and interference with oncogenic signalling pathways. However, it is important to acknowledge several limitations of the current experimental design. Firstly, the study was conducted using only one established glioblastoma cell line (T98G) and relied solely on the MTT assay for quantitative measurement of viability. The MTT assay quantifies the metabolic activity of mitochondrial dehydrogenases but does not directly determine apoptosis, necrosis, or cell-cycle effects; thus, the exact mode of cell death remains undetermined. Secondly, the authors did not perform parallel experiments with non-malignant (normal) cells, making it impossible to assess the selectivity of the extract for tumour versus normal cells based on the current data. Thirdly, plant extracts are complex mixtures, and their composition can vary depending on botanical source, harvest time, and extraction conditions. The qualitative phytochemical profile described here

does not reflect full chemical standardisation or quantification of individual bioactive constituents. Fourthly, the study was conducted in vitro, and translating these preliminary findings into therapeutic potential will necessitate further mechanistic studies (e.g., apoptosis markers, ROS measurement, pathway analysis), as well as in vivo efficacy and toxicity evaluations. Despite these limitations, the data provide preliminary evidence that Ficus carica fruit extract exhibits concentration-dependent cytotoxic activity against T98G glioblastoma cells and warrant further investigation as a potential natural source of anti-glioblastoma compounds.

4. CONCLUSION

The ethanolic extract of the fruit of Ficus carica L. shows dose-dependent in vitro cytotoxicity on T98G glioblastoma cells. All tested concentrations (0.25%, 0.5%, and 1%) significantly decreased cell viability compared with the untreated control ($p = 0.000$), with the 1% concentration having the strongest effect ($p = 0.008$ versus lower concentrations). The quantitative results of MTT were confirmed by morphological observations. However, the limitations of the single-cell-line MTT-based model, which include the lack of normal-cell control, mechanistic insight, and extract compositional variability, necessitate further mechanistic, selectivity, and in vivo studies before any therapeutic conclusions can be drawn; nonetheless, these results suggest the extract's promising anticancer potential against glioblastoma cells.

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AUTHOR CONTRIBUTIONS

Mochammad Erwin Rachman: Conceptualization, Laboratory Analysis, data interpretation, drafted the manuscript

Rosdina Bte Ladju, Andi Asadul Islam, Muhammad Nasrum Massi: Supervision, methodology, review

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Muhammad Akbar : Editing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

This research was conducted entirely in vitro using the commercially available established cell line T98G and did not involve any human participants, identifiable human biological materials, or animal subjects. Therefore, ethical approval from an Institutional Review Board or Ethics Committee was not required.

DATA AVAILABILITY STATEMENT

The raw data from the MTT assay results, which include absorbance values and the calculated cell viability percentages of T98G cells treated with Ficus carica L. fruit extract, can be obtained from the corresponding author upon reasonable request.

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